Clinical Autonomic Research (2021) 31:187–203
https://doi.org/10.1007/s10286-020-00687-0

REVIEW ARTICLE

# Exercise-based cardiac rehabilitation and parasympathetic function in patients with coronary artery disease: a systematic review and meta-analysis

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Received: 7 January 2020 / Accepted: 24 March 2020 / Published online: 8 April 2020


## Abstract

**Purpose** The effects of exercise-based cardiac rehabilitation (CR) on parasympathetic modulation are controversial. This systematic review and meta-analysis aims to (a) determine the effect of exercise-based CR on heart-rate-derived indices associated with cardiac parasympathetic modulation in resting and post-exercise conditions in coronary artery disease (CAD) patients and (b) identify the possible moderator variables of the effect of exercise-based CR on parasympathetic modulation.

**Methods** We searched CENTRAL and Web of Science up to November 2018 for the following terms: adult CAD patients, controlled exercise-based CR interventions and parasympathetic modulation measured in resting (vagal-related heart rate variability [HRV] indices of the root mean square of the differences in successive in RR interval [RMSSD] and high frequency [HF]) and post-exercise (heart rate recovery [HRR]) pre- and post-intervention. We estimated a random-effects model of standardised mean difference (SMD) and mean difference (MD) for vagal-related HRV indices and HRR, respectively. We assessed the influence of categorical and continuous variables.

**Results** The overall effect size showed significant differences in RMSSD ($SMD_+ = 0.30$; 95% confidence interval [CI] = 0.12–0.49) and HRR ($MD_+ = 5.35$; 95% CI = 4.08–6.61 bpm) in favour of the exercise-based CR group. The overall effect size showed no differences in HF between groups ($SMD_+ = 0.14$; 95% CI, −0.12–0.40). Heterogeneity analyses reached statistical significance, with high heterogeneity for HF ($p < 0.001$; $I^2 = 70\%$) and HRR ($p < 0.001$; $I^2 = 85\%$). Analysis of the moderator variables showed that the effect on HRR is greater in young patients ($p = 0.008$) and patients treated with percutaneous intervention ($p = 0.020$).

**Conclusions** Exercise-based CR improves the post-exercise parasympathetic function, with greater effects in younger CAD patients and in those who were revascularised with percutaneous intervention. The effects on resting parasympathetic function are more controversial due to methodological inconsistencies in measuring HRV, with the use of RMSSD recommended instead of HF because its results show higher consistency. Future studies involving women, focusing on methodological issues, and performing other training methods are needed to increase our knowledge about this topic.

**Keywords** Autonomic nervous system · Aerobic training · Resistance training · Acute myocardial infarction · Coronary heart disease

## Introduction

The autonomic control of cardiovascular function, assessed by heart rate variability (HRV) [1, 2] or heart rate recovery (HRR) [3, 4], is severely altered in patients with coronary artery disease (CAD) after acute myocardial infarction (AMI) or surgical intervention. Reduced HRV or HRR are strong predictors of mortality risk, sudden cardiac death or cardiac arrhythmias [5–10]. Exercise-based cardiac rehabilitation programmes (CR) improve cardiovascular mortality

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s10286-020-00687-0) contains supplementary material, which is available to authorized users.

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rates [11], cardiorespiratory fitness (CRF) and quality of life in CAD patients [12]. Although the mechanisms that underlie these beneficial effects remain speculative, the improvement of autonomic dysfunction following exercise-based CR might involve a triggering of these effects [13]. Heart rate variability is the oscillation in the interval between heartbeats; it depends on the continuous modulation of the autonomous nervous system (ANS) branches [14]: the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). Within HRV indices, the root mean square of the differences in successive RR interval (RMSSD; time domain method) and high frequency (HF; frequency domain method) are considered to be vagal-related HRV indices [15]. Heart rate recovery is defined as the difference in the heart rate (HR) between the peak of exercise and one or more minutes after exercise cessation [16]. The recovery of HR after exercise occurs due to SNS deactivation and PNS reactivation [17]. However, the first minute of recovery is predominantly determined by PNS reactivation [16, 18–20]. Although vagal-related HRV indices and HRR are parasympathetically mediated, previous studies have reported that these indices might represent independent aspects—but complementary information—with regard to PNS function [21].

However, studies that investigated the exercise-based CR-induced effect on PNS modulation often provide contradictory findings. For instance, Butz and Kober [22] and Currie et al. [23] revealed no changes in HRV and HRR after a 3- and 12-week exercise-based CR programme, respectively. Nascimento et al. [24] only found an HRR increase after exercise-based CR in patients with low functional capacity and parasympathetic activity, while Mendes et al. [25] observed an improvement in HRV following an inpatient exercise-based CR programme. Previous inconclusive findings could be due to participant characteristics (e.g. age, sex, physical fitness and/or surgical intervention) [26] and differences in the structure of the exercise-based CR programmes (e.g. wait time, exercise mode and dosage) [27]. Besides, Billman et al. [28] and Catai et al. [29] highlighted the necessity of improving HRV measurement methodologies to reach conclusive findings.

A previous meta-analysis carried out by Nolan et al. in 2008 [30] showed that exercise-based CR increases HRV, based upon a composite of time- and frequency-domain vagal-related indices (0.36; 95% confidence interval [CI] = 0.18–0.55). However, this meta-analysis did not investigate the exercise-based CR-induced effect on post-exercise PNS modulation. Notably, the authors included CAD and chronic heart failure patients without performing a subgroup analysis based on the clinical condition, and better reported and controlled trials have since been published. Therefore, in this systematic review and meta-analysis, we aim to determine the effect of exercise-based CR, compared with usual care and psychosocial and/or educational interventions, on the resting and post-exercise parasympathetic function in CAD patients and to identify the possible moderator variables of the exercise-based CR-induced effect.

## Methods

We conducted and reported a systematic review of the literature and a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. We registered the systematic review and meta-analysis protocol prospectively in the PROSPERO database (CRD42019122419).

### Data search and sources

We identified potential studies via a comprehensive strategy. We performed a systematic review in the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 11) and Web of Science (all databases) databases. We also searched conference proceedings on the Web of Science Core Collection. The search strategy involved cross-checking the selected keywords based on Medical Subjects Headings (MeSH) and free text; it was based on a previous meta-analysis [11]. We selected studies published prior to November 2018 and did not apply language restrictions during this phase (the full search strategy is presented in Online Resource 1). In addition, we hand-reviewed all full-text articles assessed for eligibility, and we contacted the authors to identify possible additional published and unpublished studies.

### Study selection

We established the eligibility criteria according to the PICOS (participants, intervention, comparisons, outcomes and study design) guideline. We included male and female adult patients (≥ 18 years) if they suffered an AMI, had a diagnosis of angina pectoris, underwent revascularisation (percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass grafting [CABG]) or had a CAD diagnosis via angiography (participants). We delineated exercise-based CR as a supervised outpatient or a home-based intervention, including aerobic training, resistance training or combined aerobic and resistance training, either alone or in addition to psychosocial and/or educational interventions. We did not impose restrictions regarding the minimal length of exercise-based CR to analyse the minimal duration of the treatment to produce changes in ANS activity (intervention). The comparison group could include usual care and psychosocial and/or educational interventions but not a structured exercise training programme (comparison).

Each selected study had to report HRV, HRR or both. For HRV, we selected only those studies that reported vagal-related HRV indices in the frequency domain (HF) or in the time domain (RMSSD); both recommended as preferential PNS measures [15]. We included studies that reported HF if power was derived from an autoregressive model (AR) or fast-Fourier transformation (FFT). Previous studies stated that both methods produce very similar estimates of HF power [32]. We included studies that measured PNS in absolute values, logarithmically transformed values or normalised units of HF. For HRR, the relevant studies measured this variable during the first minute after maximal exercise (outcomes). Finally, we included randomised and non-randomised controlled trials (study design) in English, Spanish, French or Italian. We limited the inclusion of studies with more than one article based on the same sample to only one.

Two authors (A.M. and J.M.S.) assessed all identified titles/abstracts for possible inclusion. When there was not a consensus, the article was included in the next stage for a review of the full text. The same authors reviewed the full texts of the remaining studies against the inclusion criteria. Subsequently, we settled disagreements by consensus.

## Data extraction and coding moderator variables

Two authors (A.M. and J.M.S.) independently extracted study characteristics using a standardised data extraction form. Disagreements were resolved by consensus. We classified all possible moderator characteristics as extrinsic, participant, treatment or methodological variables to measure HRV. To analyse the heterogeneity among the results of the primary studies, we calculated the mean value between the two groups in each continuous variable as a potential moderator variable for quantitative synthesis.

We coded the extrinsic and participant variables as follows: (a) year of publication; (b) country where the study was performed; (c) sample size; (d) age of the sample (years); (e) men (%); (f) AMI (%); (g) type of revascularisation surgery (PTCA, CABG or mixed); (h) left ventricular ejection fraction (%); (i) CRF ($ml \cdot kg^{-1} \cdot min^{-1}$); and (j) patients who used beta-adrenergic blocking agents (%).

We coded the following treatment variables: (a) exercise mode (aerobic, resistance or combined aerobic and resistance training); (b) aerobic training method (high-intensity interval training [HIIT] or moderate continuous training [MCT]); (c) intensity (%); (d) training frequency (days per week); (e) treatment length (weeks); (f) number of exercise sessions; (g) setting (supervised hospital/centre- or home-based); (h) implementation of extra physical activities (yes or no); and (i) wait time to start exercise-based CR after procedure or event ($< 3$ months or $\geq 3$ months).

The methodological conditions used to measure HRV were coded as follows: (a) equipment (electrocardiogram or HR monitor); (b) method used to calculate the power spectral density (AR or FFT); (c) units (normalised, logarithmically transformed, or absolute values); (d) setting (24-h ambulatory monitoring or lab-based); (e) assessment position; (f) breathing rate (spontaneous or controlled); and (g) wash-out treatment before assessments.

## Assessment of risk of bias

Using the Cochrane Collaboration's core risk of bias items, two reviewers (A.M. and J.M.S.) independently assessed the systematic risk of bias of each study included in the quantitative synthesis [33]. We resolved disagreements between these authors by consensus. We used this tool to assess the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). We classified studies as high, unclear or low risk of bias from each item based on the descriptive judgements proposed in the Cochrane Handbook [33].

## Computation of effect sizes and statistical analyses

We used the standardised mean difference (SMD) as the effect size (ES) index to assess the change in vagal-related HRV indices and the mean difference (MD) as the ES for HRR. We transformed the data into its absolute logarithmic value before calculating the SMD for the absolute HF and RMSSD values [34]. We calculated the SMD by subtracting the mean change in the exercise-based CR group from the mean change in the control group divided by the pooled standard deviation (*SD*) at baseline. We then corrected the data by a factor $c(df_{E,C})$ for small samples [35]. We classified the magnitude of the SMD as trivial ($< 0.2$), small (0.2–0.6), moderate (0.61–1.2), large (1.21–2.0) or very large ($> 2.0$) [36]. We defined the MD as the difference between the average change between the two groups. Positive values of SMD or MD indicated a favourable treatment outcome.

We performed separate analyses for each SMD or MD index according to the outcome measure to avoid statistical dependence. We applied a random-effects model for each meta-analysis, in which the mean ES was weighted by its inverse variance; the sum of the within-study variance was an estimate for the variance among studies. We used a conservative value of 0.7, previously proposed by Rosenthal [37], to calculate the variance of each study when the studies did not report the correlations between pre- and post-treatment measures. The analysis included calculating the mean ES with its 95% CI, a heterogeneity statistical test, chi-square and the $I^2$ index to evaluate the degree of homogeneity of the ESs around the average effect [38, 39]. We considered a statistically significant effect when $p \leq 0.05$.

We classified heterogeneity as low, moderate or high at 25%, 50% and 75%, respectively. We considered $I^2$ index values greater than 50% to indicate substantial heterogeneity [40]. We analysed the relationship between the ESs and the categorical and continuous moderator variables using analysis of variance (ANOVA) or subgroup analysis for categorical variables and simple meta-regressions with $Q_B$ and $Z$ statistics for continuous variables if we observed the existence of heterogeneity between the ESs. We conducted all analyses using weighted least squares and assuming mixed-effects models [41]. We also applied the above-mentioned criteria regarding heterogeneity analyses to conduct subgroup analysis.

We analysed publication bias using a funnel plot [42] and Egger's regression intercept [43]. In the case of suspected bias, we implemented a trim-and-fill method for imputing missing ESs [44]. We utilised Review Manager (RevMan) 5.3, Comprehensive Meta-Analysis 3.3 and macros for SPSS elaborated by David B. Wilson for statistical analyses.

### Sensitivity analysis

Regarding the decisions we made when obtaining our results, we examined the robustness of the meta-analytic findings related to the design and analysis decisions using sensitivity analyses [45]. We analysed the impact of including or excluding non-randomised controlled trials. In addition, we used the outlier-labelling rule [46] to check the effect of outliers in our results. We also tested the influence of using an unknown correlation for pre- and post-intervention values using analyses carried out using different supposed correlations (e.g., 0.5, 0.6, 0.8 and 0.9).

## Results

### Study selection

Figure 1 illustrates the systematic review process. In brief, from a total of 3541 studies, 45 were eligible for full-text analysis, of which we excluded 20 studies from qualitative synthesis (please see the reasons in Fig. 1) [22, 25, 47–64]. From the 25 studies included for qualitative synthesis, we included 21 for meta-analysis. We excluded four because they showed a median and interquartile range without a normal data distribution ($n=2$) [65, 66] or there was insufficient data to calculate the ES ($n=2$) [67, 68]. The studies included in the quantitative synthesis also allowed us to define 26 independent comparisons between exercise-based CR and control groups as follows: HF ($n=12$) [69–80], RMSSD ($n=5$) [73, 75–78] and HRR ($n=9$) [81–89]. Although we attempted to locate unpublished studies, all the selected studies had been published in peer-reviewed journals.

### Study characteristics

The characteristics of the studies are summarised in Table 1. The 25 included studies are from 11 countries. Seventeen studies (68%) were randomised and eight (32%) were non-randomised controlled trials. In total, there were 1346 patients (697 patients in the exercise-based CR group and 649 in the control group), with a mean age of $59.45 \pm 5.85$ years. Trial sample sizes varied from 18 to 268 patients (mean $\pm$ $SD = 53.84 \pm 50.76$ patients). Seven studies (28%) included exclusively male patients and one (4%) included only females, while 15 studies (60%) used a mixed sex sample and two (8%) did not report this information. Fourteen trials (56%) included post-AMI patients and three (12%) recruited exclusively post-revascularisation patients (CABG or PTCA). Fifteen trials (60%) reported CRF, which varied from 13.4 to 31.7 ml·kg$^{-1}$·min$^{-1}$ (mean $\pm$ $SD = 21.28 \pm 5.95$ ml·kg$^{-1}$·min$^{-1}$). The percentage of patients taking beta-adrenergic blocking agents ranged from 0 to 100% (mean $\pm$ $SD = 64.18 \pm 34.58$%), as reported by 21 trials (84%).

The treatment characteristics are reported in Table 2. Twenty-two studies (88%) compared aerobic training with control, and three (12%) compared combined aerobic and resistance training with control. Regarding the resistance training performed on the studies that combined both training methods, Chen et al. [81] performed between 12 and 15 repetitions at 40–60% of one-repetition maximum (1RM), Medeiros et al. [86] carried out 15 repetitions at 50% of 1RM, and Kalka et al. [85] included 8–10 resistance exercises and performed from 12 to 15 repetitions based on the rating of perceived exertion. Twenty-three trials (92%) applied MCT and two (8%) applied HIIT as the aerobic training method (please see aerobic intensity in Table 2). The mean weekly training frequency was three sessions per week, during an average of 12 weeks, in a supervised hospital/centre-based setting (88% of the studies). Nineteen trials (76%) started exercise-based CR within 3 months after the procedure or event, while six of them (24%) started after 3 months. The authors of three studies (12%) explicitly reported that they performed the assessments during drug wash-out [67, 70, 86].

Out of 15 trials that measured the effect of exercise-based CR on HRV, 10 (67%) reported HF and five (33%) reported HF and RMSSD (Table 1). Thirteen studies (87%) recorded the RR interval with an electrocardiogram [67–75, 77–80], and two (13%) recorded their data with an HR monitor [65, 76]. Eight trials (53%) determined power spectral density by FFT [68, 69, 71, 76–80], five (33%) by AR [67, 70, 72–74] and two (14%) did not report that information [65, 75]. Four

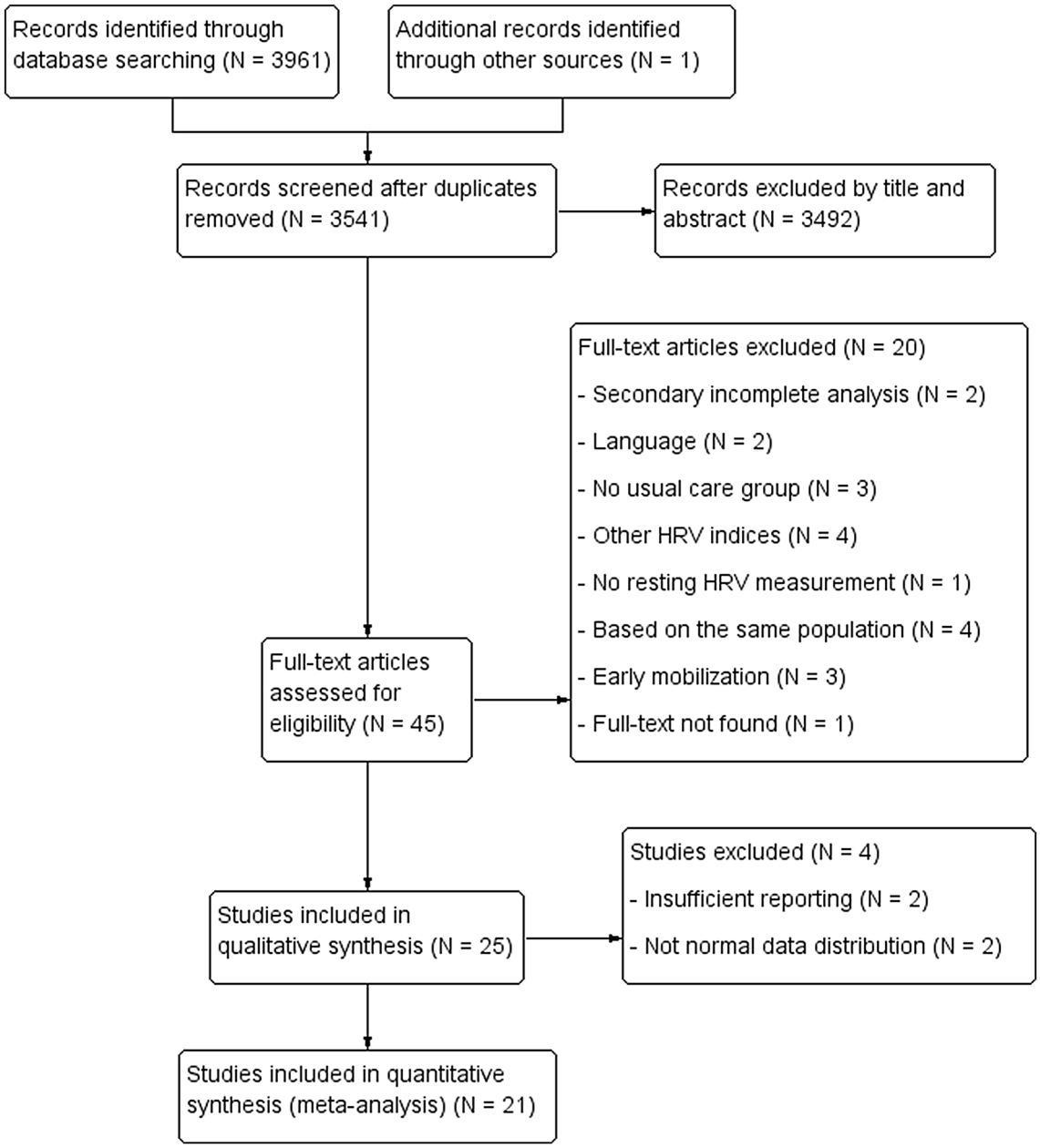


**Fig. 1** Flow chart of the study selection procedure

trials (27%) assessed HRV by 24-h ambulatory monitoring [67, 68, 75, 78] and 11 (73%) by lab-based measures [65, 69–74, 76, 77, 79, 80], mainly in a supine position (82%) [65, 69, 71–74, 76, 77, 80]. Out of the 11 studies that performed lab-based measures, seven trials (64%) allowed the patients to breathe spontaneously [69, 70, 72–74, 77, 80], three (27%) controlled the breathing rate [65, 71, 76] and one (9%) did not report that information [79].

## Risk of bias assessment

The risk of bias assessment is detailed in Online Resource 2. We judged random sequence generation and allocation concealment (selection bias) as unclear and high risk, respectively. Only two randomised controlled trials [76, 80] clearly reported details about the generation and concealment of the random allocation sequence. Only four trials blinded the outcome assessment [74, 76, 83, 88], and we judged the detection bias as high risk. However, the outcomes measured in this meta-analysis can

**Table 1** Outcome measures, subject and extrinsic characteristics

| Study (author, year) | Outcome measure | Country | *N*<br>CR / C | Age<br>(years ± *SD*) | Men (%) | AMI (%) | LVEF<br>(% ± *SD*) | CRF ($ml \cdot kg^{-1} \cdot min^{-1}$) | Beta-adrenergic blocking (%) | Revascularization procedure |
|---|---|---|---|---|---|---|---|---|---|---|
| Chen et al. [81], 2014[b] | HRR | Taiwan | 21 | 69.7 ± 4.5 | 76.0 | 71.0 | 54.1 ± 7.6 | 14.0 ± 2.5 | 71.0 | Both |
| | | | 15 | 69.0 ± 4.6 | 80.0 | 67.0 | 50.7 ± 7.1 | 14.7 ± 2.5 | 60.0 | |
| Duru et al. [69], 2000 | HF nu | Switzerland | 12 | 56.0 ± 5.0 | 100 | 100 | 32.0 ± 7.0 | 19.3 ± 3.0 | NR | Both |
| | | | 13 | 55.0 ± 7.0 | | | 33.0 ± 6.0 | NR | | |
| Fujimoto et al. [68], 1999[a] | HF ab | Japan | 20 | 59.0 ± 11.0 | 100 | 100 | 59.2 ± 7.2 | 18.1 ± 3.0 | 0.0 | PTCA |
| | | | 20 | | | | 54.3 ± 10.5 | 19.0 ± 4.0 | | |
| Giallauria et al. [83], 2011 | HRR | Italy | 37 | 61.0 ± 7.0 | 75.0 | 100 | 42.4 ± 9.9 | 16.4 ± 1.5 | 86.0 | PTCA |
| | | | 38 | 60.0 ± 8.0 | 84.0 | | 44.1 ± 8.3 | 16.7 ± 2.2 | 84.0 | |
| Giallauria et al. [82], 2006[b] | HRR | Italy | 104 | 68.0 ± 3.0 | 77.9 | 100 | 44.6 ± 2.7 | 14.7 ± 1.3 | 76.9 | NR |
| | | | 164 | 68.3 ± 3.0 | 82.9 | | 44.5 ± 2.7 | 14.4 ± 0.2 | 75.0 | |
| Kalka et al. [85], 2016[b] | HRR | Poland | 89 | 60.4 ± 9.3 | 100 | 67.8 | 57.0 ± 7.0 | NR | 94.4 | PTCA |
| | | | 35 | 61.4 ± 8.8 | | 54.3 | 55.0 ± 7.2 | | 94.3 | |
| La Rovere et al. [70], 1992 | HF nu | Italy | 18 | 47.0 ± 6.0 | 100 | 100 | NR | NR | NR | NR |
| | | | 10 | 54.0 ± 10.0 | | | | | | |
| Lai et al. [71], 2011[b] | HF nu | Taiwan | 16 | 64.2 ± 5.9 | 0.0 | 100 | > 50% | NR | 31.3 | Both |
| | | | 16 | 66.7 ± 5.3 | | | | | | |
| Lucini et al. [72], 2002[b] | HF nu | Italy | 29 | 63.0 ± 10.6 | 82.8 | 31.0 | 50.0 ± 16.2 | 18.1 ± 4.9 | 62.1 | Both |
| | | | 11 | 53.0 ± 7.9 | 72.7 | 36.4 | 51.0 ± 13.3 | 18.0 ± 3.3 | 54.5 | |
| Malfatto et al. [73], 1998[b] | HF nu<br>RMSSD ab | Italy | 20 | 53.0 ± 2.0 | NR | 100 | 56.0 ± 3.0 | NR | 100 | NR |
| | | | 14 | 53.0 ± 3.0 | | | | | | |
| Martinez et al. [74], 2011 | HF nu | Brazil | 14 | 56.0 ± 7.5 | NR | 100 | 53.0 ± 7.5 | 20.6 ± 3.7 | 100 | PTCA |
| | | | 14 | 50.0 ± 7.5 | | | 55.0 ± 7.5 | 20.4 ± 6.0 | 92.9 | |
| Mazzuero et al. [67], 1992[a] | HF ab | Italy | 22 | 50.0 ± 8.0 | NR | 100 | 49.0 ± 11.0 | NR | NR | NR |
| | | | 16 | | | | | | | |
| Medeiros et al. [86], 2018[b] | HRR | Brazil | 16 | 52.1 ± 6.5 | 100 | 100 | 43.1 ± 2.8 | 26.6 ± 3.0 | 100 | PTCA |
| | | | 11 | 50.4 ± 8.8 | | | 44.6 ± 5.2 | 30.2 ± 4.0 | | |
| Munk et al. [75], 2010 | HF ln<br>RMSSD ln | Norway | 20 | 57.7 ± 10.4 | 85.0 | 0.0 | 63.0 ± 7.0 | NR | 40.0 | PTCA |
| | | | 12 | 59.7 ± 8.5 | 83.3 | | 64.0 ± 6.0 | | 61.1 | |
| Noites et al. [66], 2017[a] | HRR | Portugal | 16 | 62.5 ± 4.6 | 81.3 | 100 | 56.0 ± 8.1 | 26.0 ± 9.6 | 100 | PTCA |
| | | | 16 | 59.5 ± 7.3 | 75.0 | | 52.0 ± 3.9 | 28.8 ± 7.3 | | |
| Oliveira et al. [76], 2014 | HF ln<br>RMSSD ab | Portugal | 47 | 54.8 ± 10.6 | 85.1 | 100 | 52.8 ± 9.5 | 27.6 ± 7.3 | 91.5 | PTCA |
| | | | 45 | 58.6 ± 10.7 | 82.2 | | 54.5 ± 7.4 | 26.9 ± 5.6 | 100 | |
| Ribeiro et al. [84], 2012 | HRR | Portugal | 20 | 54.3 ± 10.8 | 90.0 | 100 | 55.1 ± 7.7 | 30.8 ± 7.8 | 90.0 | PTCA |
| | | | 18 | 57.0 ± 7.6 | 72.2 | | 55.5 ± 6.8 | 32.6 ± 5.8 | 88.9 | |

**Table 1** (continued)

| Study (author, year) | Outcome measure | Country | *N* CR / C | Age (years ± *SD*) | Men (%) | AMI (%) | LVEF (% ± *SD*) | CRF (ml·kg$^{-1}$·min$^{-1}$) | Beta-adrenergic blocking (%) | Revascularization procedure |
|---|---|---|---|---|---|---|---|---|---|---|
| Sandercock et al. [77], 2007[b] | HF ln RMSSD ab | England | 38 | 65.6 ± 11.6 | 55.2 | 44.7 | NR | NR | 63.2 | Both |
| | | | 23 | 64.9 ± 9.0 | 60.9 | 8.7 | | | 65.2 | |
| Ståhle et al. [78], 1999 | HF ln RMSSD ln | Sweden | 27 | 71.0 ± 4.0 | 75.9 | 37.9 | NR | NR | 86.2 | Both |
| | | | 33 | 72.0 ± 5.0 | 77.8 | 22.2 | | | 88.9 | |
| Takeyama et al. [79], 2000 | HF ab | Japan | 13 | 58.8 ± 6.3 | 100 | 76.9 | 62.5 ± 12.7 | 13.1 ± 1.7 | 0.0 | CABG |
| | | | 15 | 61.7 ± 8.7 | 86.7 | 66.7 | 61.6 ± 11.1 | 13.7 ± 2.5 | | |
| Tamburus et al. [65], 2015[a] | HF nu | Brazil | 12 | 56.2 ± 7.4 | 100 | 33.3 | NR | NR | 58.3 | Both |
| | | | 12 | 60.4 ± 6.1 | | 20.0 | | | 50.0 | |
| Tsai et al. [80], 2006 | HF ln | Taiwan | 34 | 57.1 ± 8.9 | 85.3 | 5.9 | 62.4 ± 11.1 | 18.3 ± 5.3 | 76.5 | PTCA |
| | | | 33 | 56.8 ± 9.9 | 75.8 | 15.2 | 61.3 ± 10.0 | 17.9 ± 4.5 | 66.7 | |
| Tsai et al. [87], 2005 | HRR | Taiwan | 15 | 61.2 ± 9.5 | NR | 0.0 | NR | NR | 0.0 | CABG |
| | | | 15 | 63.2 ± 14.6 | | | | | | |
| Wu et al. [88], 2006 | HRR | Taiwan | 18 | 62.8 ± 6.9 | 100 | 0.0 | 50.6 ± 2.1 | 15.7 ± 3.9 | 27.8 | CABG |
| | | | 18 | 62.2 ± 9.6 | | | 50.7 ± 2.4 | 16.0 ± 4.2 | 22.2 | |
| Zheng et al. [89], 2008 | HRR | China | 27 | NR | NR | 100 | > 45 | 12.6 ± 1.5 | NR | PTCA |
| | | | 30 | | | | | 11.7 ± 1.9 | | |

*ab* absolute units, *AMI* acute myocardial infartion, *CABG* coronary artery bypass grafting, *C* control group, *CR* exercise-based cardiac rehabilitation group, *CRF* cardiorespiratory fitness, *HF* high-frequency, *HRR* heart rate recovery, *ln* natural logarithm, *LVEF* left ventricular ejection fraction, *N* number of patients included, *NR* not reported, *nu* normalised units, *PTCA* percutaneous transluminal coronary angioplasty, *RMSSD* root mean square of successive differences in RR interval, *SD* standard deviation

[a]Study excluded from the meta-analysis but included for the qualitative synthesis

[b]Non-randomised controlled trial

**Table 2** Treatment characteristics

| Study (author) | Exercise mode | Aerobic training method/ intensity | Frequency (days a week) / treatment length (weeks) | Number of exercise sessions | Application mode | Wait time |
|---|---|---|---|---|---|---|
| Chen et al. [81][b] | CT | MCT / 60–80% HRreserve | 3 / 12 | 36 | Supervised | L |
| Duru et al. [69] | AT | MCT / 70% HRreserve | 4 / 8 | 32 | Supervised | S |
| Fujimoto et al. [68][a] | AT | MCT / 80% AnT | 7 / 2 | 14 | Supervised | S |
| Giallauria et al. [83] | AT | MCT / 60–70% $VO_2$ peak | 3 / 24 | 72 | Supervised | S |
| Giallauria et al. [82][b] | AT | MCT / 60% $VO_2$ peak | 3 / 12 | 36 | Supervised | S |
| Kalka et al. [85][b] | CT | MCT / 40–70% PO peak | 5 / 24 | 120 | Supervised | L |
| La Rovere et al. [70] | AT | MCT / 75–95% AnT | NR / 4 | NR | Supervised | S |
| Lai et al. [71][b] | AT | MCT / 13–15 RPE | 3 / 8 | 24 | Home-based | L |
| Lucini et al. [72][b] | AT | MCT / 70–85% HRm | 3 / 12 | 36 | Supervised | S |
| Malfatto et al. [73][b] | AT | MCT / 80% HRm | 5 / 8 | 40 | Supervised | S |
| Martinez et al. [74] | AT | MCT / 100% AnT (HR) | 3 / 24 | 72 | Supervised | S |
| Mazzuero et al. [67] | AT | MCT / NR | 3 / 24 | 72 | Supervised | S |
| Medeiros et al. [86][b] | CT | MCT / 60–75% HRt | 2 / 12 | 24 | Supervised | S |
| Munk et al. [75] | AT | HIIT / 3×4 min > 85% HRm (recovery NR) | 3 / 24 | 72 | NR | S |
| Noites et al. [66][a] | AT | MCT / 60–70% HRp | 3 / 8 | 24 | Home-based | L |
| Oliveira et al. [76] | AT | MCT / 70–85% HRm | 3 / 8 | 24 | Supervised | S |
| Ribeiro et al. [84] | AT | MCT / 65–75% HRm | 3 / 8 | 24 | Supervised | S |
| Sandercock et al. [77][b] | AT | MCT / 70% HRm* | 1 / 8 | 8 | Supervised | L |
| Stâhle et al. [78] | AT | HIIT / 4×4 min 90–95% HRp (recovery 3 min 50–70% HRp) | 3 / 12 | 36 | Supervised | S |
| Takeyama et al. [79] | AT | MCT /AnT | 7 / 2 | 14 | Supervised | S |
| Tamburus et al. [65][a] | AT | MCT / 80–110% AnT (PO) | 3 / 16 | 48 | Supervised | L |
| Tsai et al. [80] | AT | MCT / 60–85% HRreserve | 3 / 8 | 24 | Supervised | S |
| Tsai et al. [87] | AT | MCT / 60–85% HRp | 3 / 12 | 36 | Supervised | S |
| Wu et al. [88] | AT | MCT / 60–85% HRp | 3 / 12 | 36 | Supervised | S |
| Zheng et al. [89] | AT | MCT / AnT ($VO_2$) | 3 / 24 | 72 | Supervised | S |

*AT* aerobic training, *AnT* anaerobic threshold, *CT* combined aerobic and resistance training, *HIIT* high-intensity interval training, *HR* heart rate, *HRm* maximal heart rate, *HRp* heart rate peak, *HRreserve* heart rate reserve, *HRt* heart rate target, *L* wait time longer than or equal to 3 months, *MCT* moderate continuous training, *NR* not reported, *PO* power output, *RPE* rating of perceived exertion, *S* wait time less than 3 months, $VO_2$ oxygen uptake

*Shuttle-walking test

[a]Study excluded from the meta-analysis but included for the qualitative synthesis

[b]Non-randomised controlled trial

be considered to be objective, a finding that reduces the risk of detection bias. Finally, we considered attrition and reporting bias to represent an unclear risk.

## Outcomes

### Resting HRV

Pooled analysis revealed no statistically significant differences ($p = 0.290$) in HF between groups, and the overall SMD reached a trivial effect ($SMD_+ = 0.14$; 95% CI = −0.12–0.40; Fig. 2). The heterogeneity was statistically significant ($p < 0.001$) for HF, and the inconsistency was moderate (70%). According to meta-regressions (Online Resource 3) and subgroup analyses (Online Resource 4), none of the analysed variables were statistically related to the ES magnitude ($p > 0.05$) for HF. The inconsistency was moderate for the type of intervention surgery ($I^2 = 59.4\%$) and wait time to start exercise-based CR ($I^2 = 48.9\%$).

The pooled analysis showed statistical differences ($p = 0.001$) in RMSSD between groups in favour of the exercise-based CR group, and the overall SMD reached a small effect ($SMD_+ = 0.30$; 95% CI = 0.12–0.49; Fig. 3). The heterogeneity was not statistically significant ($p = 0.430$) for RMSSD; we did not identify inconsistency (0%).

## HRR

The pooled analysis revealed statistically significant differences ($p < 0.001$) in HRR between groups, with higher values in the exercise-based CR group ($MD_+ = 5.35$; 95% CI = 4.08–6.61 bpm; Fig. 4). The heterogeneity was statistically significant ($p < 0.001$), and the inconsistency was high (85%). Therefore, we analysed moderator variables. The meta-regression findings revealed that the mean age of the patients was inversely related to the ES magnitude

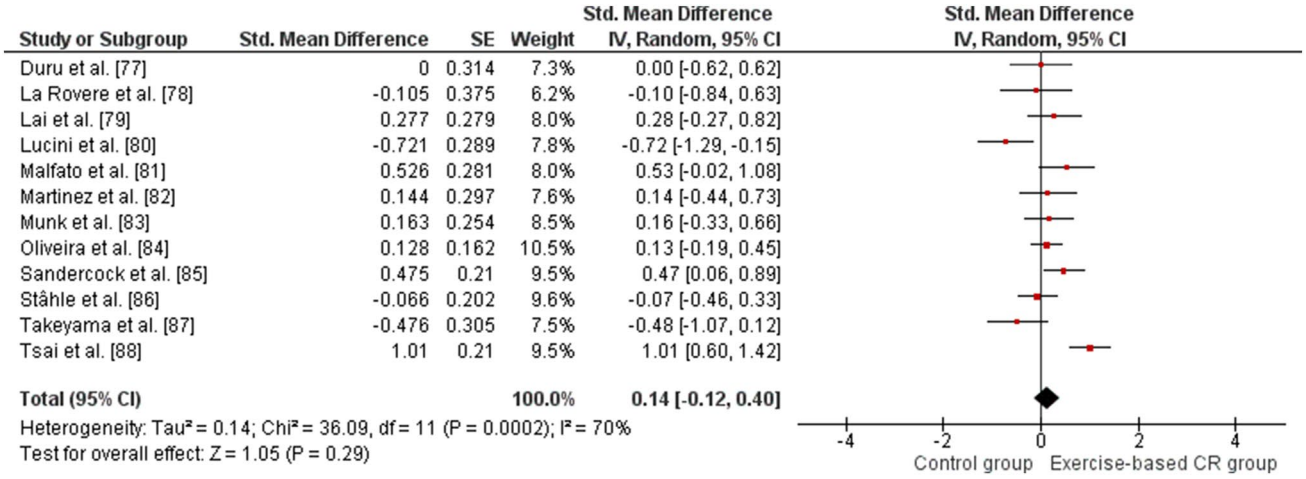


**Fig. 2** Forest plot of standardised mean difference indices for high frequency (HF)

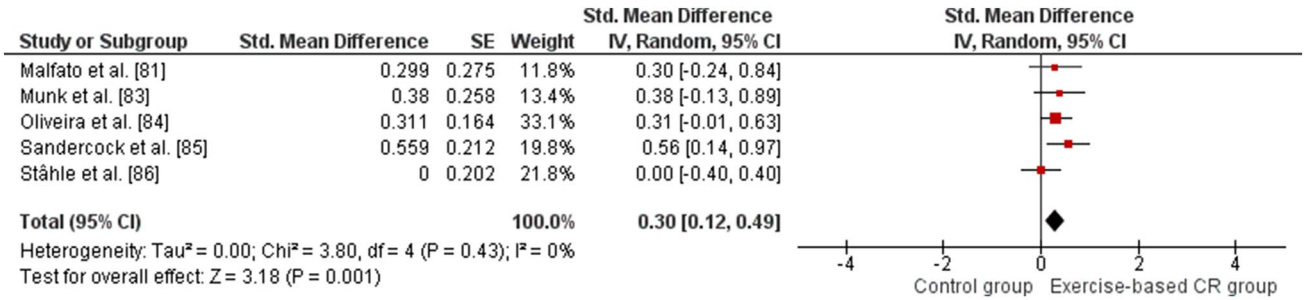


**Fig. 3** Forest plot of standardised mean difference indices for root mean square of the differences in successive in RR interval (RMSSD)

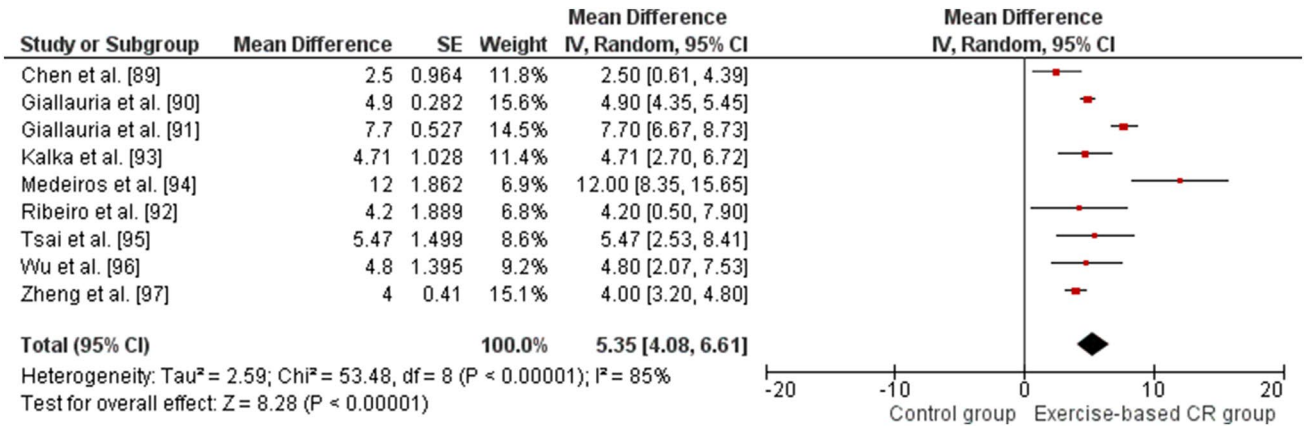


**Fig. 4** Forest plot of mean difference indices for heart rate recovery (HRR)

($p = 0.008$; Online Resource 5). The subgroup analysis for HRR (Online Resource 6) showed significant between-group heterogeneity, with high inconsistency for the type of intervention surgery procedure ($p = 0.020$; $I^2 = 75.6\%$). For wait time to start exercise-based CR, there was no significant between-group heterogeneity and moderate inconsistency ($p = 0.080$; $I^2 = 66.7\%$). There were greater differences for exercise-based CR in patients who underwent PTCA surgery ($MD_+ = 7.04$; 95% CI = 4.40–9.68 bpm) compared with CABG patients ($MD_+ = 5.11$; 95% CI = 3.11–7.11 bpm) or both conditions ($MD_+ = 2.50$; 95% CI = 0.61–4.39 bpm). In addition, patients who started to receive exercise-based CR within the first 3 months after the event showed a higher effect ($MD_+ = 5.89$; 95% CI = 4.42–7.35 bpm) than those who had to wait at least 3 months ($MD_+ = 3.58$; 95% CI = 1.41–5.74 bpm).

### Sensitivity analysis

After removing the non-randomised controlled trials for HF [71–73, 77], RMSSD [73, 77] and HRR [81, 82, 85, 86], the results did not change. We did not identify outliers for HF and RMSSD, a finding that obviated the need to assess the overall effect after removing outliers. The analysis was performed after removing an outlier (MD = 12.00) [86] for HRR (lower critical value: MD = 0.37; upper critical value: MD = 10.31). Notwithstanding a decrease in the overall ES (from $MD_+ = 5.35$; 95% CI = 4.08–6.61 bpm to $MD_+ = 4.87$; 95% CI = 3.71–6.04 bpm), the result was similar to that observed before removing the outlier. The results for HF, RMSSD and HRR did not change when using different supposed correlations between pre- and post-intervention values (0.5, 0.6, 0.8 and 0.9).

## Publication bias

We did not find evidence of asymmetry in the funnel plots for HF, RMSSD and HRR, and the Egger tests were not statistically significant (HF, $t(11) = -0.922$, $p = 0.378$; RMSSD, $t(4) = 0.230$, $p = 0.833$; HRR, $t(8) = 0.469$, $p = 0.653$). Thus, publication bias can be discarded as a threat against the findings of the current meta-analysis on a reasonable basis. The funnel plots for HF, RMSSD and HRR are presented in Online Resources 7–9, respectively.

## Discussion

This systematic review with a meta-analysis assessed the effect of exercise-based CR on resting and post-exercise measures of the parasympathetic function in patients with CAD. Our main results indicate that exercise-based CR improves both post-exercise HRR (5.35; 95% CI = 4.08–6.61 bpm) and RMSSD (0.30; 95% CI = 0.12–0.49), a resting measure of parasympathetic function. Besides, the exercise-based CR-induced effect on the post-exercise parasympathetic function was inversely related to the participant age ($p = 0.008$), and patients treated with PTCA achieved a greater improvement after exercise-based CR ($p = 0.020$).

### Resting HRV

Although HF and RMSSD are vagal-related HRV indices [13, 90], we found contradictory results according to the variable used to reflect the exercise-based CR-induced effect on the resting PNS function. Our findings showed an increase in RMSSD after exercise-based CR, without the influence of moderator variables, while we did not observe any significant changes or high heterogeneity in HF alterations.

Because of the high inconsistency ($I^2 = 70\%$) observed, we carried out heterogeneity analyses to explain these controversial findings. These analyses included patient characteristics that have been previously reported as potential moderator variables of cardiac autonomic control. For instance, previous studies reported that ageing and low physical fitness are related to a decline in parasympathetic control of the heart [91–93]. Nevertheless, proper management of training variables (i.e., intensity, frequency and duration) in exercise training would allow the induction of positive autonomic adaptations in older patients [94]. There is also evidence that both cardiac autonomic modulation [95, 96] and the exercise-based CR-induced effect on PNS status [97, 98] are influenced by sex. Although there are widely reported differences in autonomic control based on the patient and exercise-based CR programme characteristics, our findings showed no influence of these potential moderator variables on the HF changes. Similarly, previous meta-analyses did not identify an influence of participant and treatment characteristics on vagal-related HRV indices in cardiac patients [30] and older participants [99].

Another issue that might determine HRV changes after exercise-based CR is the patients' myocardial injury state. Two characteristics could be primarily related to injury state: the type of revascularisation surgery and wait time to start exercise-based CR after the procedure or event. Regarding the surgery type, the combined effect of surgical manipulation on the heart, anaesthesia and cardioplegia during CABG surgery can produce a worse heart condition after surgery compared with the PTCA procedure [14]. In fact, previous studies have reported that CABG seems to lead to higher and more prolonged autonomic dysfunction compared with PTCA [100, 101]. Regarding wait time, it is well known that early repression of the inflammatory response is essential to reducing the affected myocardial area after

AMI [102]. Besides, a shorter wait time before commencing exercise-based CR is related to greater improvements in cardiac function [103] and left ventricular remodelling [104]. Overall, this phenomenon highlights the importance of considering the wait time before starting exercise-based CR and the type of intervention surgery to correctly interpret the results of empirical studies. Santos-Hiss et al. [62] performed a 5-day phase I exercise-based CR programme based on low-intensity exercise following AMI; they reported an increase in HF values after this short exercise-based CR programme. Badrov et al. [105] reported no HF changes following a delayed ($68 \pm 11$ days following hospital discharge) 6-month exercise-based CR programme based on aerobic and resistance training. Thus, delaying the start of exercise-based CR might limit the exercise-based CR-induced effect on this variable. Szmigielska et al. [106] investigated the effect of an 8-week exercise-based CR programme on HRV indices in men treated with PTCA or CABG. The authors reported that exercise-based CR seems to be more effective for improving HRV values in CABG than in PTCA patients, but they did not find a difference in HF changes between CABG and PTCA. Although our findings showed no influence of the wait time to start exercise-based CR and the type of intervention surgery on the effect of exercise-based CR on HF values, a very small number of the included studies involved exclusively CABG patients. Besides, the wait time to start exercise-based CR was dichotomised because most of the studies did not report the mean time to start exercise-based CR after the event. Notably, dichotomisation might create considerable loss of power and residual confounding [107]. Thus, we attempted to use the original scale of the remaining variables.

The methodological aspects related to the assessment of HRV should also be considered to explain, at least partially, our results. The status of the ANS is highly sensitive to environmental factors and respiratory influences [108]. In addition, previous studies have reported that HRV indices show a natural day-to-day variation [109]. Thus, the use of the long-term daily HRV recording values helps to reduce noise and might be more consistent with regard to reflecting PNS function compared with a single-day record [110, 111]. Buchheit [108] reported that time domain indices, specifically RMSSD, have lower sensitivity to breathing patterns and day-to-day variability than spectral indices. Similarly, previous studies reported that when frequency domain indices are used, it is necessary to normalise the breathing rate to control respiratory sinus arrhythmia [112, 113]. However, all the studies included in our meta-analysis reported HRV values based on a single data point. Besides, among studies that used HF as a vagal-related HRV index, only two specified that they collected data by controlling the breathing rate [71, 76]. Therefore, similar to our findings, methodological inconsistencies in measuring HRV might have a greater impact on the results of studies that use HF as vagal-related HRV index. The impact of these methodological inconsistencies on HF values has also been identified in previous meta-analyses performed with healthy people [26] and endurance-trained athletes [114]. Current evidence seems to suggest that RMSSD might be more suitable than HF to reflect resting PNS function, because RMSSD is less affected by respiratory influences and methodological limitations.

In conclusion, methodological issues, including the lack of breathing control and the use of a single data point to reflect the PNS status, might explain our inconclusive findings and the high heterogeneity in studies that used HF as a vagal-related index in the resting condition. Thus, we recommend using time domain indices, specifically RMSSD, to study the exercise-based CR-induced effect on the PNS status. Future studies that use frequency domain indices should also consider these methodological issues to confidently reflect the resting PNS function in CAD patients. Subsequently, researchers could investigate the influence of moderator variables on the exercise-based CR-induced effect to design exercise-based CR programmes focused on improving autonomic function.

### HRR

To the best of our knowledge, this meta-analysis is the first to assess the exercise-based CR-induced effect on post-exercise PNS function in CAD patients. Nine studies reported an overall statistically relevant ES of 5.35 bpm (ranging from 2.50 to 12.00 bpm) in favour of the exercise-based CR group. Therefore, in accordance with studies carried out in other populations [115, 116], our findings showed that exercise training improves post-exercise PNS function in patients with CAD. In previous studies, delayed HRR was a strong predictor of mortality [5], and improvement in the post-exercise PNS modulation might exert a protective effect on the cardiovascular system [117]. This outcome could help to reduce mortality risk in CAD patients [118].

In contrast to what happened with HF, analyses of moderator variables demonstrated a crucial influence of the age of patients and the type of intervention surgery, as well as a possible influence of the CRF and the wait time to start exercise-based CR, on the exercise-based CR-induced effect on the post-exercise PNS function.

We found that ageing adversely affects the capacity to improve PNS function after exercise. This result supports the findings of a meta-analysis performed with healthy people, in which the authors reported that physiological ageing is correlated with a decreased trainability of the heart [26]. Although the CRF analysis did not reach statistical significance, our result showed a residual direct relationship between this variable and the exercise-based CR-induced

effect on HRR ($p = 0.066$). Beckie et al. [119] carried out a 12-week exercise-based CR programme with 236 female CAD patients. Consistent with our findings, those authors reported that CRF and age are associated with the exercise-based CR-induced effect on HRR. Regarding the type of intervention surgery, our findings showed a higher effect in patients who underwent PTCA. This result is contrary to what would be expected based on the post-surgery evolution of the patient [101]. However, to the best of our knowledge, no previous studies have investigated whether the exercise-based CR-induced effect on HRR might differ based on the type of intervention surgery.

Our subgroup analysis based on the wait time to commence exercise-based CR showed a considerable heterogeneity between categories, with higher HRR improvement in patients who waited less than 3 months to start exercise-based CR. This result is consistent with previous studies that reported that a shorter time to start exercise-based CR might lead to better improvement after CR [102, 103]. Although the analysis did not reach statistical significance, as previously noted, the wait time to start exercise-based CR was dichotomised. This factor might reduce the power considerably.

Finally, the small number of studies that analysed the influence of the CRF, performed with patients who waited 3 or more months to start exercise-based CR or with CABG patients, warrants future research to understand the influence of these variables on the exercise-based CR-induced effect on the post-exercise PNS reactivation. Thus, ageing, type of intervention surgery, CRF and wait time to start exercise-based CR might underlie the heterogeneity we identified in the included studies.

Regarding exercise-based CR programme characteristics, the subgroup analysis according to the exercise mode revealed no ES differences between aerobic training and combined aerobic and resistance training. This finding indicates that the exercise mode does not influence the effect of exercise-based CR on the post-exercise PNS function. However, no studies analysed the effect of resistance training alone. On the other hand, we did not include an analysis on the aerobic training method (HIIT versus MCT), because all the included studies applied MCT. Pattyn et al. [120] performed a meta-analysis to compare the effect of MCT and HIIT on peak oxygen uptake in cardiac patients (CAD and chronic heart failure patients). They also compared the effect of the two aerobic training methods on HRR as a secondary outcome. Their subgroup analysis based on underlying pathology revealed no differences ($p = 0.760$) between HIIT and MCT with regard to elevated post-exercise PNS function in CAD patients.

Several limitations to the previously mentioned analyses might explain why we did not identify an influence of any exercise variable on the exercise-based CR-induced effect on PNS modulation. Further, previous studies have reported that different forms and dosages of exercise (e.g. intensity, volume, training frequency) can elicit variable effects on the PNS function [27]. Aerobic training has received the most attention by researchers (88% of included studies), and it is already considered an important stimulus for increasing PNS tone [121]. Therefore, future studies should analyse the influence of other exercise modes (resistance training and combined aerobic and resistance training), as well as the effect of HIIT, and then analyse the influence of the different dosages of exercise on the exercise-based CR-induced effect on PNS function in CAD patients.

In conclusion, HRR seems to be a good method for measuring the exercise-based CR-induced effect on post-exercise PNS reactivation. However, variables like the age and CRF of patients, as well as the type of surgery that patients underwent and the time from the event until the beginning of exercise-based CR, should be considered—all of these variables might influence the results.

## Strengths and limitations

This systematic review and meta-analysis is the first to analyse the effect of exercise-based CR on resting and post-exercise PNS function with an exclusive focus on CAD patients. In addition, our analyses were performed based on the characteristics of the patients and exercise-based CR programmes. However, there are some limitations. There was significant heterogeneity between study protocols and treatment effects. Our analyses exhibited moderate-to-high evidence of heterogeneity among studies, and therefore the results must be interpreted cautiously. In most of the randomised controlled trials, the generation and concealment of random allocation sequences was poorly reported, a factor that increased the risk of selection bias in our results. Although we performed subgroup analyses, some groups had a relatively small number of studies. This fact limited the scope and power of these analyses. In addition, subgroup analysis based on the exercise mode or aerobic training method were limited because we did not include studies that performed resistance training in the meta-analysis—and only two studies used HIIT for aerobic training. Thus, we could not properly analyse the influence of these training variables on the effect of exercise-based CR on resting and post-exercise PNS function in CAD patients.

## Conclusion

Our findings demonstrated that exercise-based CR improves the post-exercise parasympathetic function in CAD patients, with a greater enhancement in younger patients and patients

treated with PTCA. However, deriving a definitive conclusion about the exercise-based CR-induced effect on resting parasympathetic function is difficult due to methodological inconsistencies in measuring HRV, mainly for studies that used HF. In this sense, our results showed a relevant increase in RMSSD; this finding suggests that exercise-based CR improves resting parasympathetic function. At the same time, the HF measure seems to be less consistent with regard to resting parasympathetic adaptations in CAD patients. We recommend the use of RMSSD instead of HF because its results show greater consistency—despite the methodological differences among studies. However, the conclusions of this meta-analysis should be limited to the effect of aerobic training, carried out by MCT, on the parasympathetic function in male patients with CAD. Future high-quality studies should involve women, focus on methodological aspects of HRV measures and perform resistance or high-intensity training exclusively to increase knowledge about the effect of exercise-based CR on resting parasympathetic modulation.

**Funding** Preparation of this article was not supported by any association or institution. Agustín Manresa-Rocamora was supported by a pre-doctoral grant given by the Ministerio de Educación, Cultura y Deporte, Spain (FPU17/01825).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** This article was a meta-analysis and therefore did not require separate human ethics approval.

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